

REMARKS**Status of the Claims**

Claims 1-29, 31, 32, 34, 36, and 38-44 are pending in this application while 39-43 are withdrawn from consideration. Claims 1-29, 31, 32, 34, 36, 38, and 44 stand rejected. The claims undergoing examination have been canceled and have been replaced by new claims 45-79. Of the new claims, only claim 1 was changed from the last version presented for examination: the other new claims correspond to claims that were presented previously, and have only been changed to correct their dependency as necessitated by the renumbering that resulted from replacing the previous versions claims with new claims. Previous claim 1 is presented as new claim 45, and has been amended to describe “determining if a fluorescence emission from the first semiconductor nanocrystal occurs.” This is supported by the specification, see e.g. page 4, and by original claim 23. No new matter is added by the amendments. Reconsideration of the claims in view of the following remarks is respectfully requested.

Noncompliant Amendment Issues

The Examiner noted that noncompliant amendments were submitted earlier. The Applicants regret the issues identified with those amendments, and appreciate the tolerance extended by the Examiner during prosecution. Applicants believe that the instant Amendment is fully responsive to all points, and corrects any issues with earlier claim amendments. In particular, rejections of all claims are addressed by the discussion below, and the previously entered and examined claims have been replaced with a new set of claims. The claims are based on and correspond to the previous ones, but they have been retyped out of necessity. They also have been proofread and are believed to correspond to claims presented earlier, but none are identified as Original because all are considered new. The new claims correspond to previously examined claims as summarized in the table provided below for the Examiner’s convenience. Prior to the filing of the instant Amendment, Applicants attempted to contact the Examiner via telephone in an effort to ensure that all of the Examiner’s concerns are fully addressed by the new claims submitted

herewith. Should the Examiner deem it necessary, however, Applicants will re-submit the previous amendments with corrected claims on request.

The Examiner also noted certain clerical errors in the previous response, whereby certain claims were not explicitly addressed, or claims appear to have been misidentified when discussed. The Applicants appreciate the Examiner's understanding, and the continued prosecution. The Applicants do not see that these errors rise to the level of rendering the Amendment non-compliant, since the Examiner was able to understand what was intended; and no Notice of Noncompliance was sent to the Applicants. Nevertheless, the Applicants greatly appreciate the Examiner's cooperation despite errors made in the response. The following Table is provided to clarify how the new claims relate to those most recently entered and examined:

Original Claim No.	New Claim No.	Is new claim amended relative to the last version presented?
1	45	YES: added "determining if a fluorescence emission from the first semiconductor nanocrystal occurs."
2	46	No
3	47	No
4	48	No
5	49	No
6	50	No
7	51	No
8	52	No
9	53	No
10	54	No

Original Claim No.	New Claim No.	Is new claim amended relative to the last version presented?
11	55	No
12	56	No
13	57	No
14	58	No
15	59	No
16	60	No
17	61	No
18	62	No
19	63	No
20	64	No
21	65	No
22	66	No
23	67	No
24	68	No
25	69	No
26	70	No
27	71	No
28	72	No
29	73	No

Original Claim No.	New Claim No.	Is new claim amended relative to the last version presented?
30	Canceled	Canceled
31	74	No
32	75	No
33	Canceled	Canceled
34	76	No
35	Canceled	Canceled
36	77	No
37	Canceled	Canceled
38	78	No
39	Withdrawn	Unchanged
40	Withdrawn	Unchanged
41	Withdrawn	Unchanged
42	Withdrawn	Unchanged
43	Withdrawn	Unchanged
44	79	No

The sole outstanding grounds for rejection is based on allegations of obviousness. The basis for each rejection and the cited references have been carefully considered, and the following comments are offered in response. In view of these remarks, the Applicants believe all rejections are overcome, and the claims are in condition for allowance.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-5, 14-15, 17-19, 23-28, 31-32, 34, 36, 38, and 44 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Mirkin et al (WO98/04740) in view of Pinkel et al (5,690,894) and further in view of Weiss et al (5,990,479.) The Examiner said this about Mirkin:

In a single exemplary embodiment, Mirkin et al teach providing a substrate attached to a first target; namely, a substrate comprising a plurality of initial type of oligonucleotides attached to the substrate in an array of spots, wherein each spot contains a different type of oligonucleotide (page 40, line 30-page 41, line 11). The plurality of different initial type of oligonucleotides attached in an array of spots is the claimed plurality of different targets attached to a substrate. Because there are different types of targets, each target can preferentially bind to a corresponding different probe polynucleotide. The substrate is contacted with the first sample, wherein the first sample is suspected of comprising the first probe; namely, analyte DNA is added to the substrate (Figure 13B); the instantly claimed "first probe" is the analyte DNA of Figure 13B, and the instantly claimed 'targets' are the adsorbed thiol modified DNA of Figure 13B. The first probe comprises a first probe polynucleotide comprising a first tag sequence which does not bind to the first target and a first binding sequence which does bind to the first target, and wherein contacting the substrate with the first sample takes place under conditions in which the first binding sequence can bind to the first target; namely, Figure 13B shows part of the first probe hybridizing to the immobilized targets through a first binding sequence, and the remainder of the first probe is a first tag sequence available to bind to DNA modified nanoparticles. The DNA modified nanoparticles of Figure 13B are the tag-binding conjugate, which binds to the first tag sequence. The nanoparticles are a semiconductor nanoparticles (page 19, lines 24-34), and determining if the semiconductor nanocrystal is associated with the substrate occurs because Mirkin et al teach color changes resulting from binding on the substrate where noted (page 83, lines 18-20 and Figure 13B, last step).

(Emphasis added). The Applicants traverse this rejection for the following reasons.

Mirkin does not use a semiconductor nanoparticle.

The Examiner's summary of Mirkin indicates that Example 13B uses a semiconductor nanoparticle; that is not correct. The Examiner pointed to and relied upon Figure 13B as basis for the rejection. In the statement of rejection, the Examiner said, "The DNA modified nanoparticles of Figure 13B are

the tag-binding conjugate, which binds to the first tag sequence. The nanoparticles are a semiconductor nanoparticles (page 19, lines 24-34)...” However, Figure 13B expressly states that its first layer of nanoparticles are ‘gold nanoparticles.’ There appears to be no reason to doubt that its remaining nanoparticles are also gold nanoparticles, and good reason to believe that they are gold nanoparticles—e.g., Mirkin states that gold nanoparticles are “preferred for use in detecting nucleic acids” (page 20, lines 25-28) and it states that use of gold nanoparticles for this application “results in an immediate color change visible to the naked eye (see, e.g., Examples.)” (page 21, first two lines). Contrary to the Examiner’s position, the example from Mirkin thus does not use a semiconductor nanocrystal as required by the claim; it uses a gold particle, and a person of ordinary skill would certainly recognize gold as a conductive material rather than a semiconductor.

Mirkin states that gold nanoparticles are “preferred for use in detecting nucleic acids.” Page 20, lines 25-28. It states that use of gold nanoparticles for this application “results in an immediate color change visible to the naked eye (see, e.g., Examples.)” Page 21, lines 1-2. The Examiner pointed to a passage where Mirkin generally refers to a large variety of nanoparticles that could in principle be used (pg. 19, line 24-pg. 20, line 24); however, the Example relied upon by the Examiner does not use a semiconductor nanoparticle. Indeed, it appears that Mirkin does not ever use a semiconductor nanoparticle, and its *stated preference* is for a gold nanoparticle. The rejection is thus based on a misinterpretation of the reference, and is thus improper.

No reason to modify Mirkin to use a semiconductor nanoparticle was shown.

The rejection as stated would require one to modify Mirkin’s examples, and it would require moving away from Mirkin’s preferred nanoparticle. Since the Examiner misinterpreted Example 13B in Mirkin, no reason for modifying it was provided. The modification of Mirkin’s examples that would be required to suggest using a semiconductor nanoparticle was made without explanation or justification. While it may be reasonable in some circumstances to modify the reference’s teachings in such fashion, the Office has the burden to show that such changes are justified. In this case, the Office needs to show that a person of ordinary skill would have had motivation to select something else besides the preferred gold nanoparticle; that the person would have chosen a

semiconductor nanoparticle as required in the claims; and that in doing so the person of ordinary skill would have retained a reasonable expectation of success. That has not been done, so the rejection is improper. Nor would it suffice to rely upon the fact that the reference includes a semiconductor nanoparticle among the list of particles that *could* be used; the reference discloses many options for its nanoparticle, and it discloses a preference for a particular one that is not a semiconductor. Selecting one of many options disclosed cannot be done to support a rejection without a reason—that would be evidence that the substitution was being made solely in hindsight, rather than from the perspective of the person of ordinary skill in the art, whose actions must be considered at a time point before the present application, and thus without reference to the present disclosures.

It has been held that a different item can be substituted for one used in a reference when making a rejection, but only where the equivalence of the substitute has been recognized in the art. MPEP 2144.06(II): (“In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). (The mere fact that components are claimed as members of a Markush group cannot be relied upon to establish the equivalency of these components. However, an applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist.)” (emphases added)) The alternative types of nanoparticles mentioned as possible ones in Mirkin are analogous to a Markush group; they are merely disclosed as alternatives to the gold nanoparticles that Mirkin actually used, and their treatment in an obviousness analysis should be similar. In the present case, there is no evidence that a semiconductor nanoparticle would be equivalent to a gold nanoparticle; and the reference itself teaches nonequivalence, by stating a preference for the gold nanoparticle.

Mirkin teaches a preference for and advantages of its gold nanoparticles that would be lost with a semiconductor nanoparticle.

Indeed, the Mirkin reference boasts that using its gold particles permits one to see a positive result with the naked eye; the semiconductor nanoparticles were not shown to provide this feature or to offer any identified advantage over the preferred gold nanoparticles. In view of this, no *prima facie* case for an obviousness rejection has been shown, because the rationale relied upon by the Office is not properly supported by Mirkin's examples or its stated preference for gold nanoparticles.

Pinkel was mischaracterized in the rejection.

In addition, the Examiner stated that Mirkin fails to disclose "separate determination of each binding event." To address this deficiency, the Examiner relied upon Pinkel. According to the Examiner,

Pinkel et al teach a method of assaying samples for probes by using a biosensor array to detect nucleic acid binding complexes (Abstract), wherein each binding event is separately determined; namely, simultaneous assaying of binding components of a test sample are done on by discretely [sic] detection at individual locations (i.e., bundles of fibers; Abstract). Thus, Pinkel et al teach the known technique of separately determining each binding even on an array.

The Examiner concludes that "it would have been obvious to the ordinary artisan that the known technique of using the separate determination of each binding event on an array of Pinkel et al could have been applied to the method of Mirkin with predictable results because the separate determination of Pinkel et al predictably results in detection of all of the binding events during a microarray hybridization assay."

Respectfully, the Applicants assert that the characterization of Pinkel is not supported. The rejection points solely to the abstract of Pinkel, and says it discloses "using a biosensor array to detect nucleic acid binding complexes." In fact, the only reference in the Abstract to a nucleic acid is Pinkel's statement about its biosensor having 'binding partners' that bind other molecules to form a binding complex. One of the several complexes can be a nucleic acid—nucleic acid complex.

Respectfully, this general mention of nucleic acid-nucleic acid binding complexes does not disclose a biosensor array being used to detect nucleic acid binding complexes as the Examiner suggests; it merely provides a general list of binding complexes of various types that can be used on optical fiber biosensors.

Because Pinkel is so different from Mirkin, it is irrelevant to the reasonable expectation of success for Mirkin's system.

In addition, the Examiner said the person of ordinary skill would have a 'reasonable expectation of success' with modifying Mirkin, because the "separate determination of Pinkel et al predictably results in detection of all of the binding events during a microarray hybridization assay." It is not clear how this statement is supported by the Pinkel Abstract; regardless, though, Pinkel uses a different technology that was not shown to be analogous to or predictive of what can be done with Mirkin's technology. Pinkel uses an array of optical fibers adapted as biosensors (its term) to analyze a 'test sample' (Abstract); it does not relate to nanoparticles or targets on a substrate. It is simply irrelevant to the 'reasonable expectation of success' in the present obviousness analysis. Regardless of what might be done by or with Pinkel's array of optical fibers / biosensors, Mirkin is not using an array of optical fibers or anything that would normally be characterized as a biosensor. Thus Pinkel's alleged success does not provide a reasonable expectation of success for the modification of Mirkin's system that the rejection relies upon. Because Mirkin's system is so different, the person of ordinary skill would not look to Pinkel's system to decide how to modify Mirkin's system, and would not draw any conclusion about whether Mirkin's system could be modified accordingly.

Weiss was not shown to overcome the deficiencies of Mirkin and Pinkel.

The Examiner purported to establish the rejection of claim 1 based on these references combined with a third reference, Weiss, alleging that it would have been obvious "to have modified the method comprising the use of semiconductor nanocrystals as taught by Mirkin et al and Pinkel et al with different nanocrystals as taught by Weiss et al with a reasonable expectation of success..."

Thus Weiss is relied upon for the use of 'different nanocrystals'. As stated above, the use of 'different nanocrystals' in an obviousness rejection is appropriate where the art recognizes that the substituted item is equivalent to the one which is to be replaced / substituted. As pointed out above, Mirkin's example used a gold nanoparticle, and Mirkin states and provides reasons for a preference for using gold nanoparticles. Semiconductor nanoparticles were not shown to be equivalent to what Mirkin used; accordingly, an obviousness rejection that relies upon substitution of other nanoparticles for the gold nanoparticles that Mirkin used, without justification for that change, is improper. Nothing in the rejection shows that Weiss overcomes the deficiencies of Mirkin and Pinkel.

Summary of Rebuttal of the rejection based on Mirkin and Pinkel.

The rejection of claim 1 relies upon a misinterpretation of Mirkin: the Examiner stated that Mirkin's example used a semiconductor nanoparticle, and that is not supported by the reference. Mirkin used a gold nanoparticle in the Example 13B: there is no evidence that it used a semiconductor nanoparticle for such methods, and Mirkin says the gold nanoparticle was preferred. The rejection appears to be based on the applicant's disclosure of a method using a semiconductor nanoparticle; it is not based on what Mirkin did or on what one of ordinary skill would have done based on the Mirkin reference. This is evidence of improper hindsight analysis. For this reason alone, the rejection is improper and should be withdrawn.

The rejection as presented would require the person of ordinary skill to modify Mirkin by using a semiconductor nanoparticle. The Applicants are aware that the reference must be considered for all it discloses, but that does NOT mean that all alternatives and combinations that can be created by selecting features or terms at random from the reference are 'obvious.' Obviousness is properly determined from the perspective of a person of ordinary skill, without knowledge of the present invention. The reference's express disclosure of a preference for a gold nanoparticle would have been important to the person of ordinary skill: it is an important part of what the reference discloses and *cannot* be ignored. As discussed above, the substitution of a semiconductor for the gold nanoparticle that Mirkin used in the Examples is inconsistent with the reference's stated preference

for a gold nanoparticle; or, put another way, this modification relies upon a selection from among many alternative nanoparticles disclosed in Mirkin, and the selection was done without justification. No reason was provided for the person of ordinary skill to modify the reference in this way, giving up the operable gold nanoparticle method, which provided immediate visualization of results with the naked eye. Therefore, a rejection has not been properly established, because the rejection does not show why a person of ordinary skill would have used a semiconductor nanoparticle as required by the claim. Nothing in the rejection shows that Weiss or Pinkel overcomes the deficiencies of Mirkin. For this additional reason, the rejection should be withdrawn.

In addition, the combination with Pinkel is improper because it alleges that Pinkel discloses something that is not in the cited passage of the reference: the Abstract is a generalized statement that does not describe the biosensor being used. Contrary to what was stated in the rejection, Pinkel's Abstract does not describe "using a biosensor array to detect nucleic acid binding complexes." Moreover, the rejection relies upon Pinkel to allege that a person of ordinary skill modifying Mirkin would have had a 'reasonable expectation of success'; yet the technology at issue is so different from that in Pinkel, that one of ordinary skill would not consider Pinkel relevant to a 'reasonable expectation of success' with modified versions of Mirkin's methods. The differences in technology are substantial, so whether or not Pinkel works to achieve a certain result is just not informative about what would happen if one modified Mirkin. Nothing in the rejection shows that Weiss overcomes the deficiencies of Mirkin and Pinkel. For this additional reason, the rejections based on Mirkin and Pinkel should be withdrawn.

The modification of Mirkin changes its mode of operation, which is impermissible in an obviousness rejection.

As pointed out before, the Examiner misinterpreted Mirkin: Mirkin's examples use a gold nanoparticle, not a semiconductor nanoparticle. Mirkin's Example 13B demonstrates how gold nanoparticles can be caused to aggregate upon a first nanoparticle that binds to a substrate where an

immobilized sequence is present. It illustrates how Mirkin's method provides a dark or colored spot visible to the naked eye.

In order to convert Mirkin, which is the base reference in this rejection, into the claimed invention one must substitute semiconductor nanoparticles for Mirkin's preferred gold particles. The semiconductor nanoparticles are visualized quite differently; they require a system suitable for fluorescence detection. This was clear to one of ordinary skill in claim 1 as previously presented, because it described the different fluorescence characteristics used to observe the semiconductor nanocrystals; and it is reinforced in the claims as presented. The claim corresponding to previous claim 1 (new claim 45) has been amended to describe "determining if a fluorescence emission from the first semiconductor nanocrystal occurs." That limitation is supported by original claim 23 and throughout the specification and examples, e.g. at page 4. To practice the claimed invention, one must modify what Example 13B of Mirkin discloses by using a different nanoparticle in place of Mirkin's gold nanoparticle, and also by using a different visualization method, rather than Mirkin's amplification process that permits direct visual observation of a dark spot or color change. The changes modify the basic operating principle by which Mirkin detects a binding event. Such changes to the mode of operation of a base reference are improper in an obviousness rejection. MPEP 2143.01(VI), citing *In re Riatti*, 270 F2d 810, 123 USPQ 349 (CCPA 1959).

Rejections of dependent claims.

The rejection of claim 1, as applicable to new claim 45 that corresponds to previous claim 1, is overcome for the reasons presented above. All of the other claims under examination depend from and thus include all limitations of claim 45. All of the rejections of these dependent claims rely upon the above-discussed rejection of claim 1 based on Mirkin, Pinkel and Weiss. Therefore, all of the rejections of claims depending from claim 45 are also overcome; these claims are allowable over the cited art because they include all limitations of a claim that is allowable over the cited art, and the rejection presented no basis to show that the additional references cited overcome the deficiencies noted above with regard to the characterization and application of Mirkin, Pinkel and Weiss to claim 45.

For the reasons set forth above, all claims under examination are believed to be allowable. Reconsideration and withdrawal of those rejections are respectfully requested.

CONCLUSION

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (760)-268-8490. In the event additional fees are required, applicants hereby authorize the Commissioner to charge these fees or credit any overpayment associated with this or any other filing to **Deposit Account No. 50-3994**.

Respectfully submitted,

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/Joseph Taffy/
Joseph Taffy
Reg. No. 50,973

Invitrogen Corporation
Customer No. 23358
Phone: (760) 268-8490
Facsimile: (760) 476-6048